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Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061

ROCKVILLE, MARYLAND 20852
USA

Docket No. 98D-0994; Draft Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Post-approval Changes: Chemistry, Manufacturing and Controls (CMC) Documentation; Notice of Availability Appearing in the Federal Register of November 30, 1998 (63FR65793)

Dear Sir/Madam

Merck KGaA is a manufacturer of active ingredients for drug products since 1827. We supply customers throughout the world including the USA. We have been inspected regularly by the FDA since 1968.

Therefore we are affected by the "Draft Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Post-approval Changes: Chemistry, Manufacturing and Controls (CMC) Documentation".

We appreciate very much the opportunity to provide comments on this important draft guidance for industry.

Sincerely,
Merck KGaA
i.V. i.A.

Walter Dr. Sinz

98D-0994

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C32 1/1

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Attachment

Docket No. 98D-0994; BACPAC I:

General Comments

We understand that the changes covered by BACPAC I only encompass changes in the information filed in the approved application.

It should be sufficient to prove the equivalence by comparing three postmodification batches to three recent premodification batches. Equivalence is demonstrated if impurities are within the stated limits of the specification or if not specified at or below the upper statistical limit of historical data. When equivalence is proven before the final intermediate filing the change in an annual report should be sufficient.

All BACPAC I changes should be reported to the FDA and the drug product manufacturer. However the drug product manufacturer should not be obliged to file a CBE supplement or an annual report for such changes, since the drug substance quality is not affected. Furthermore, if an API intermediate manufacturer supplies other API manufacturers or drug product manufacturers it does not make good economic or scientific sense for the FDA to have to assess several NDAs which all reference the same change made by one API manufacturer in one DMF.

Changes made prior to the final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effected supplement is suggested.

Specific comments

p. 2, line 17-20
Postapproval changes affecting (1) ~~**synthetic peptides**~~, (2) oligonucleotides, (3) radiopharmaceuticals, or (4) drug substances derived exclusively by isolation from natural sources or produced **exclusively** by procedures involving biotechnology are not addressed in this document.
Synthetic peptides should be within the scope of BACPAC I as there is no principle difference between peptides and other drug substances produced by organic synthesis.

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p .4, line 95-97
~~**For example, if the drug substance is a mixture of isomers, then the same quantitative mixture should be obtained after the change.**~~
This sentence should be deleted as it is covered by the general equivalence requirement.

p. 5, line 123-124
The level of impurities should be assessed by comparing three postmodification batches to **three** ~~**ten**~~ premodification ~~**commercial**~~ batches.
(see general comments)

p. 5, line 128-130
The impurity profile will be considered equivalent after a given change if at least three postmodification batches of either an isolated **(or *in situ*, if appropriately justified)** intermediate or the drug substance are evaluated and the test data demonstrate that for:
The demonstration of equivalence may take place at an in situ intermediate if appropriate justification is provided:

p. 5, line 137-138
Existing impurities, including residual solvents if relevant, ~~**are at or below the upper statistical limit of historical data**~~ are within the approved specification or, if not specified, are at or below the upper statistical limit of historical data.

p. 5, line 139
Total impurities are **within the stated limits, or, if not specified**, are at or blow the upper statistical limit of historical data.

p. 6, line 149-150
Existing impurities, including organic solvents **if relevant**, are within the stated limits, or, if not specified, are at or blow the upper statistical limit of historical data.

p. 6, line 159
~~**In situ intermediates are generally not appropriate for demonstrating equivalence.**~~
In situ intermediates, if appropriately specified, should be treated as isolated intermediates.

p. 7, line 200
Conformance to historical ~~**particle size distribution profile**~~ **specification**.

p. 8, lines 227-229
Site changes within a single facility **or within a contiguous campus** that fall within the scope of sections IV.A and IV.A1 need not be filed with the Agency and equivalance testing as described in this document nedd not be carried out.

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p. 8, lines 266
~~**Changes being effected**~~ **Annual Report** supplement if
For changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effectied supplement is suggested.

p. 10/11, lines 275-276
Scale changes include increases and decreases in the batch size of the intermediates including the final intermediate **in cases where the equipment geometry may have an influence on the reaction**.

p. 11, line 330
Specification changes made to comply with compendial changes **or adoption of limits of compendia including broadening of the own historical limit**.

p. 14, lines 395
~~**Changes being effected**~~ **Annual report**.
For changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effected supplement is suggested.

p. 15, line 442
~~**Changes being effected supplement.**~~ **Annual report.**
For changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effected supplement is suggested.

p. 17, line 480
~~**Prior approval supplement.**~~ **Annual report.**
For changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effected supplement is suggested.

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Not all options available to all destinations

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